REMARKS

By this Amendment, claims 5, 9, 13, 14 and 49 are amended. Claims 1, 3-10, 12-19, 21-35, 48 and 49 are pending in this Application. Support for the amendments can be found in the previous claims. No issue of new matter arises.

Claim objections

Claims 9 and 49 were objected to. Claims 9 and 49 are amended above to correct the typographic errors. Reconsideration and withdrawal of this objection are respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

Claim 5 was rejected relating to the placement of commas in "lymphoid tissue type, follicular reticulum cell sarcoma". Claim 5 is amended delete this phasing. No issue of new matter arises. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 13 was rejected based on recitation of autoimmune disease. The Examiner opines that autoimmune disease are undefined because some disease are not known to be autoimmune' but might be. Whether a disease is autoimmune is a matter of fact that should be decided by a jury or judge using available evidence. Because a disease may later be recognized to be autoimmune does not imply that autoimmune is without meaning. . Although Applicants strongly disagree that a term so used in the art could be the basis of such rejection, claim 13 is amended to delete this allegedly undefined recitation. Claim 14 is amended for proper dependency. No issue of new matter arises. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph: enablement

Claims 3-10, 12-19, 21 and 49 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The rejection was presented in four parts.

I. Claims 4-10 relating to treatment of cancerous hyperproliferative disorders.

II. Claims 12-14 relating to non-cancerous hyperproliferative disorders.

III. Claim 3 Treatment of both

IV. Claims 15, 16, 18, 19 and 21 relating to apoptosis.

The Examiner appears to rely on a per se rule that treatment of cancers and hyperproliferative disorders cannot be considered enabled. The Office Action argues that treating hyperproliferative disorders and preventing or suppressing apoptosis are opposing utilities.

Apoptosis is characterized by the Examiner as the body's most powerful anti-tumor mechanism. Induction of apoptosis is alleged as the mechanism of action of drugs such as paclitaxel and tamoxifen. But such effect cannot be absolute if they were completely successful in inducing apoptosis the organism would not survive, all the cells having died a programmed death. The point of this is that treatment is relative and measured. So while some apoptosis may be advantageous or desired at certain times, apoptosis is not always required in every cell.

In the present situation, if cells do not cycle, they do not proliferate. Dead cells also do not proliferate. The effect is the same. Just because cycling is required for apoptosis and cycling is also required for proliferation merely serves to show the broad applicability of the present invention. The Examiner alleges that suppressing apoptosis would make no sense. However, the Examiner recognizes that resistance to apoptosis may be the most important determinant of tumor resistance. Accordingly, logic would indicate that another mechanism might be desired for these tumors. If proliferation could be impeded, tumor growth would be slowed. Other tools might also be applied such as radiation to further slow tumor growth or even to kill cells. Also it must be realized that tumors are complex structures. Depending on tumor type there may be oxygen depleted zones; other cell types, not cancerous can be recruited to supply the tumor, e.g., endothelial cells for blood delivery. These different cell types would be expected to display different behaviors when confronted with drugs. For example the present inventive compounds were required because similar compounds in the art preferentially partitioned in red blood cells. The Examiner does not see a similarity in that two processes may require one or more common pathways or elements. For example, both apoptosis and proliferation require transcription. Water is essential for life, but may cause drowning. Yet no one advocates water deprivation to save lives. The Examiner then concedes that whether he understands that two processes can share a similar pathway is not at issue. He concludes that based on the belief that apoptosis is essential to counter tumors, suppressing apoptosis would make matters worse. Applicants once again get back to balance, that events must be measured and balanced. Especially for tumors resistant to apoptosis, interfering with cell cycling thereby inhibiting proliferation would logically be an advantage and would not make the cancer worse. With respect to autoimmune disorder, since the Examiner is not sure what these are and to

expedite allowance of the present application the claims as amended no longer recite autoimmune disease. This issue is thereby mooted.

The Office Action then goes back to treating cancers generally. Several cases are presented that each present their own facts. The facts of the present invention include inhibition of a pathway known to be involved in all cancers. The case descriptions provided by the Examiner are nice snippets, but just that: sound bites by themselves with no particular tie to the instant fact situation.

Applicants respectfully recognize that the Examiner feels bound by case law. However, the case law must be properly applied. In this instance, the Examiner misses the boat. The Examiner has not cited a case where a common mechanism was recognized and cannot reasonably be disputed. Inhibiting that common mechanism is at the heart of the present invention. The broad applications that the present invention may be useful for cannot be refuted. The case law cited by the Examiner did not include discussion of facts indicating that exemplary results though expected to be applicable across a broader range than the court allowed, would not be persuasive. The expectation that inhibiting proliferation, a process common to all cancers, would have an effect on cancers in general cannot be rationally refuted. Expectation is all we learn from science. Given certain experimental results a hypothesis is either more or less likely.

Wands is cited. The Examiner argues that one factor includes the number of compounds, but fails to provide any evidence why any of the claimed compounds would not function as claimed. Thus this factor provides no help to the allegation of lack of enablement. Apparently the Examiner misunderstood Applicants remarks. Applicants apologize for any misunderstanding. Applicants indeed did not stop the remarks regarding enablement at that point, by "numbers alone". Applicants meant that without indication that any one of the compounds could not me made or used as claimed, the number of compounds usable had no relevance to an enablement rejection. Moreover if a rare instance were to be found where the compound might not function the general class of compounds claimed would still be enabled so long as undue experimentation were not required to find the next working example.

The Examiner questioned the number of compounds which was taken by Applicants as an implication that they might be inferred to lack commonality of action. The discussion of –Z-Ra makes clear that the result of the claimed –Z-Ra groups is reduced basicity of the nitrogen. Basicity of the nitrogen has been shown to be an important determinant of uptake of these compounds by red cells. Applicants do not see where they argue against the notion that the featured –Z-Ra groups

achieve the noted result. Applicants respectfully request the Examiner to expand this discussion if the Examiner wishes to maintain this aspect of the rejection. The examiner questioned how function of a recited sidegroup relates to enablement. Perhaps the Examiner is missing the point. Enablement relates to a requirement for undue experimentation. While the Examiner questioned the number of possible -Z-Ra groups, as apparently relevant. The Examiner does not make the connection that if each member of the group has the same effect, then that would speak for the examples being demonstrative of the group. Indeed the molecule as a whole is important. Applicants do not disagree. However, functionality of some functions of the compound is more tolerant of different structure than other portions of the compound. In the business end that has the business of interacting with the CDKs, only minor variations are claimed in comparison to a portion that controls uptake by the red blood cell. On the CDK side any event is desired. A close match is apparently required to bind the CDK. However, since basicity of the –Z-Ra nitrogen seems to be controlling for preventing RBC uptake and many molecular groups can achieve the desired effect, a large variety of groups can be used here. Despite the number of possibilities to achieve the same effect, each member of the recited group would be expected to function in an enabling fashion. Thus this issue cannot properly be cited as indicative of lack of enablement.

In part (1)(b) of the Office Action, Breadth of claims, The Examiner provided a long list of diseases, yet no evidence or even allegation is presented that these disease do not involve hyperproliferation and cell cycling. There is no discussion why inhibition of CDKs as claimed would not be beneficial in treating these diseases. Hence, although the number is large, there is no stated reason to doubt enablement. Without a stated reason, Applicants' evidence of CDK inhibition and the known involvement of CDKs in the disease process speak for rather than against enablement.

On page 27 part (2) predictability is discussed. Applicants counter that CDK inhibition has predictable results. Cell cycling stops and so does proliferation. Thus predictability is on the side fro rather than against enablement. The Examiner refuses to recognize progress and cites case dicta (not law) referencing unpredictability of anti-cancer treatment. The Examiner refuses to recognize significant progress in the field since President Nixon declared war on cancer and started massive funding increases. This funded research has born fruit. Cancer and cancer treatment are not unpredictable as they might have properly been characterized in the late 1960s or early 70s. The Examiner has misplaced precedent. The reference to unpredictability can only be seen as dicta. It is

a statement of the times, at that time in the 70s. Though the Federal Circuit adopted law as decided by the CCPA as precedential, facts or dicta are not precedent and need not and indeed should not, especially when shown to be inapplicable, be relied upon. Applicants respectfully request that the Examiner reconsider this aspect of the rejection in a rational fashion.

At part (30, the Examiner discusses Direction or Guidance. The Examiner bases this rejection on the generic range of dosage for the compounds. Applicants respectfully submit that a generic range is proper in view of the narrow target range of the compounds. These compounds bind CDKs. Depending on the degree of inhibition dosage can be titrated with only routine, not undue experimentation. The Examiner stands by drugs that have foundered for lack of a working dosage regimen. The Examiner again refers to foundering because of lack of dosage regime that "actually works". No rational being would believe that experiments would continue to find a dosage regime if the compound was without effect. The Examiner in fact indicated that these drugs were promising. There must have been evidence that they worked at some dosage. The problem that could not be overcome probably related to solubility, volume, side effects, classes of hypersensitive individuals or the like. Once again the Examiner in his admission the "Many" drugs foundered recognizes the routine nature of the research involved. In such applications while failures may occur they are routine because of the great possibilities offered by success. With so much to gain the experimentation quite obviously was not undue but merely routine.

At part (4) the Examiner again seems to be implying that new discoveries or inventions if not obvious are not enabled. Such is not the law in these United States where rule of law and a strong patent system have provided means to great national wealth.

The present compounds are shown to inhibit CDKs and CDKs are recognized as important pathways in identified diseases. Antiproliferative effect is shown in the application. The diseases are antiproliferative diseases. Applicants do not have to piggyback on other compounds to prove the effect of the present compounds.

The Examiner cited Knockaert for its mention that cellular targets at that time were yet to be identified. Cellular targets of what? Compounds shown to be potent inhibitors of CDKs! Specific knowledge of cellular targets is quite apparently not required to reach a nanomolar IC_{50} level! Thus a reading of Knockeart shows the lengths the Examiner is forced to stretch to attempt to maintain this rejection. Knockart as a whole supports enablement rather than argues against it. A single statement with unknown meaning taken out of context is not proper justification for any rejection.

At part (5) working examples are discussed. While Applicants believe that arguments of record are sufficient to overcome this rejection should an appeal be necessary, Applicants question whether this rejection applies to claims 22, 23 and 49. Indication one way or the other may reduce issues is appeal proves necessary.

At part (6) the Examiner discusses skill in the art. The Examiner supports enablement by indicating that although the list is large the list elements share a commonality of involving one or more types of hyperproliferation. See page 34. In the next paragraph, the Examiner states the length of a list he can craft is relevant to enablement because scope of the claims is an element for consideration in an enablement rejection. Applicants do not agree, length of a list does not matter. Merely being able to name embodiments and sub-embodiments and include more or less lengthy descriptions in not determinative of scope. Scope of this aspect of the invention is rather concise, hyperproliferative diseases. All the members of the list, according to the Examiner involve hyperproliferation. Compounds of the present invention are shown to inhibit hyperproliferation, thus the scope is covered and despite any lsist the claimed invention is enabled. What aspect of hyperproliferation inhibited by the compounds of the present invention is not within the elements of the Examiner's list? None, as so stated by the Examiner. Clearly this aspect of the rejection lacks sound basis.

In the Office action around page 36 the Examiner steps into the shoes of the FDA. While treatment is claimed, nowhere do the claims state an FDA approvable treatment. Success in the clinic while it may be demonstrative of enablement cannot properly be cited against the present claims. Nowhere does patent law require demonstrated or likelihood of commercial success before a patent is granted. The standard for enablement is a requirement for undue experimentation. Nowhere in this lengthy Office Action is such a requirement shown.

With respect to autoimmune disease, such recitation is removed form the claims. The scope of the claims was not intended to include autoimmune diseases that did not involve hyperproliferation. This aspect of the rejection is thus mooted.

The lack of seriousness the Examiner places in this application is demonstrated at page 49 of the Office action. The Examiner ignores Applicants' correction or the typographic error which omitted the word "not". The Examiner harkens back to the previous reply in which the mistake was made. The Examiner is respectfully requested to consider all arguments Applicant puts forth including correction of past misstatement or errors.

The Examiner also errs in his application of 35 USC §102 and/or 35 USC §103 to 35 USC §112 rejections. Anticipation is clear. A species is patentable over a genus, but one species in a claimed genus is anticipatory. Applicants do not disagree. But if that is the Examiner's only point why is it in an Office Action where no 35 USC §102 or 35 USC §103 rejection is made. Applicants still do not understand. An explanation of relevance to the instant application is respectfully requested. The fact remains that the majority of the embodiments in Wands, the case the Examiner cites as basis for the enablement rejection, were inoperative embodiments. This goes to emphasize that possible existence of one or more inoperative embodiments is not proper basis fro rejection. A requirement for undue experimentation is the legal standard.

Since no requirement for undue experimentation is found in the Examiner's Action Applicants respectfully request reconsideration and withdrawal of the rejection. Should the Examiner wish to maintain the rejection in whole or in part, applicants request indication by the Examiner of which aspects of the rejection apply to which claims and indication of which claims or parts thereof may be, in the Examiner's opinion, enabled.

Double Patenting

Applicants gratefully acknowledge the Examiner's indication of a double patenting issue. However, the claims have yet been deemed allowable, the final form and number of the claims that might issue in this application is unknown. A terminal disclaimer at this time is premature as any claim(s) that might issue may or may not be deemed obvious over claims 1-10 of USP 6,861,524. Applicants go on record to correct the Examiner's statement that method claims are not patentably distinct from compound claims. Applicants do not admit this allegation by the Examiner. The Examiner is plainly incorrect in this blanket statement.

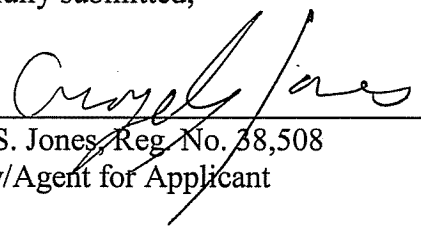
Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt indication of such. Should the Examiner wish to suggest additional amendments that might place the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

Respectfully submitted,



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